EXHIBIT 1, Tab 14

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Articles

Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial

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Summary

Background Phase II trials of leflunomide, an inhibitor of de-novo pyrimidine synthesis, have shown efficacy in rheumatoid arthritis. This double-blind randomised trial compared leflunomide with placebo and sulphasalazine in active rheumatoid arthritis.

Methods 358 patients were randomly assigned leflunomide (100 mg daily on days 1–3, then 20 mg daily), placebo, or sulphasalazine (0·5 g daily, titrated progressively to 2·0 g daily at week 4). The primary endpoints were tender and swollen joint counts and investigator's and patient's overall assessments. Analyses were by intention to treat.

Findings The mean changes in the leflunomide, placebo, and sulphasalazine groups were −9·7, −4·3, and −8·1 for tender joint count; −7·2, −3·4, and −6·2 for swollen joint count; −1·1, −0·3, and −1·0 for physician's overall assessment; and −1·1, −0·4, and −1·1 for patient's overall assessment. Leflunomide and sulphasalazine were significantly superior to placebo ($p=0·0001$ for joint counts; $p<0·001$ for assessments). Radiographic disease progression was significantly slower with leflunomide and sulphasalazine than with placebo ($p<0·01$). Most common adverse events with leflunomide were diarrhoea (17%), nausea (10%), alopecia (8%), and rash (10%). Transiently abnormal liver function was seen in three leflunomide-group patients and five sulphasalazine-group patients. There were two cases of reversible agranulocytosis in the sulphasalazine group.

Interpretation Leflunomide was more effective than placebo in treatment of rheumatoid arthritis and showed similar efficacy to sulphasalazine. Leflunomide was well tolerated. This drug may be a useful option as a disease-modifying antirheumatic drug.

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Introduction

Rheumatoid arthritis is a progressive disease associated with severe morbidity, functional decline, permanent disability, and an increase in mortality.[1] Disease progression is rapid in the early phases.[2,3] There has therefore been a growing trend for early, aggressive treatment with disease-modifying antirheumatic drugs (DMARDs).[4] A recent investigation found consistent use of DMARDs in patients with moderate or long-standing rheumatoid arthritis.[5] However, only a few DMARDs have been unequivocally shown to retard radiographically assessed disease progression;[6,7] sulphasalazine is one of these DMARDs.[8–12] Furthermore, DMARDs can rarely be given for long periods in rheumatoid arthritis owing to lack of sustained efficacy or to toxicity.[10,13,14] Therefore, there is a need for new agents with a high ratio of efficacy to toxicity that decrease clinical signs and symptoms of rheumatoid arthritis, retard disease progression, prevent new joint erosions, and improve functional ability and quality of life.

The primary action of leflunomide, an immunomodulatory agent, is inhibition of de-novo pyrimidine synthesis by selective inhibition of dihydro-orotate dehydrogenase, a key enzyme in the process.[15–17] Cells such as activated T lymphocytes that predominantly synthesise pyrimidines via the de-novo pathway seem to be especially sensitive to the effect of leflunomide.[17] Hypotheses on the pathogenesis of rheumatoid arthritis invoke an important role of activated T lymphocytes.[18–20]

Leflunomide effectively inhibits the progression of arthritis in studies in animals, including the rat adjuvant and the MRL/lpr mouse models.[21] The efficacy and safety of leflunomide were investigated in comparison with placebo in a dose-finding phase II study of patients with rheumatoid arthritis.[22] Although DMARDs show better efficacy than placebo, they can differ in their efficacy and toxicity profiles.[8,10,14] We therefore undertook a phase III study to compare leflunomide with placebo and with sulphasalazine, a DMARD known to be effective,[8–12] in the management of patients with active rheumatoid arthritis.

Patients and methods

Patients

Eligible participants had a diagnosis of active rheumatoid arthritis based on the revised criteria of the American College of Rheumatology[23] and were of functional class I, II, or III, according to the classification of the American College of Rheumatology. Active disease was defined by the presence of six or more tender joints, and six or more swollen joints, based on 28-joint count;[24] overall assessments by the physician and patient of rheumatoid arthritis activity as fair, poor, or very poor; C-reactive protein (CRP) 20 mg/L or higher (normal less than

	Leflunomide (n=133)	Placebo (n=92)	Sulphasalazine (n=133)
Demographic characteristics			
Mean (SD) age (years)	58·3 (10·6)	58·8 (12·2)	58·9 (11·4)
M/F	32 (24%)/ 101 (76%)	23 (25%)/ 69 (75%)	41 (31%)/ 92 (69%)
Duration of rheumatoid arthritis			
Mean (SD) duration (years)	7·6 (8·6)	5·7 (6·5)	7·4 (10·0)
Number with duration ≤2 years	50 (38%)	41 (45%)	56 (42%)
Number with duration >2 years	83 (62%)	51 (55%)	77 (58%)
Number with no previous DMARD treatment	53 (40%)	49 (53%)	68 (51%)
Number of ACR functional class			
I	10 (8%)	3 (3%)	6 (5%)
II	74 (56%)	50 (54%)	76 (57%)
III	49 (37%)	39 (42%)	51 (38%)
Clinical			
Rheumatoid-factor positive	105 (79%)	76 (83%)	106 (80%)
Concomitant corticosteroids	38 (29%)	23 (25%)	37 (28%)
Concomitant NSAIDs	113 (85%)	76 (83%)	109 (82%)

ACR=American College of Rheumatology.

Table 1: **Baseline characteristics of participants**

10 mg/L); or erythrocyte sedimentation rate (ESR) 28 mm/h or higher. The study protocol required that sulphasalazine therapy (well tolerated and for 2 months or less) had been discontinued at least a year before enrolment. None of the patients in the sulphasalazine group, two in the leflunomide group, and one in the placebo group had received sulphasalazine previously. The protocol also required that treatment with all other DMARDs had been discontinued at least 28 days before enrolment. Consenting patients, aged 18 years or older, were required to use adequate methods of contraception, and women of childbearing potential had to have a blood test to exclude pregnancy before enrolment.

Study design

This multinational, randomised, double-blind, placebo-controlled study took place in 36 centres in Australia, Austria, Belgium, Denmark, Germany, the Netherlands, New Zealand, Norway, Slovenia, South Africa, Sweden, and the UK. Appropriate ethics committee approval was obtained for each centre. After a 1-week screening period, patients, stratified by duration of rheumatoid arthritis (≤2 years or >2 years), were randomly assigned in a ratio of three/three/two to groups that would receive leflunomide (n=133), sulphasalazine (n=133), or placebo (n=92). Double-blind treatment with leflunomide began with a loading dose of 100 mg daily on days 1–3, followed by 20 mg daily for the remainder of the study.[25] For sulphasalazine, an enteric-coated preparation was given at doses of 0·5 g, 1·0 g, and 1·5 g once or twice daily during weeks 1, 2, and 3, respectively, and 2·0 g daily during weeks 4–24. The dose of 2·0 g daily has been widely used;[8–10,12] it is favoured as a standard dose for initial and, for most patients, for continuing therapy.[26] Placebos to both leflunomide and sulphasalazine were used in a double-blind technique to preserve allocation concealment. Randomisation was generated centrally by computer and was site specific. After week 4, at the discretion of the investigator, doses could be lowered for patients who had clinically significant adverse events or haematological or biochemical abnormalities; the dose of leflunomide could be decreased from 20 mg to 10 mg and that of sulphasalazine from 2·0 g to 1·5 g. The lower dose was then maintained until the end of the study.

Non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, and oral corticosteroids (≤10 mg prednisolone or its equivalent) were allowed at daily doses that had been constant for at least 30 days before study enrolment. Intra-articular steroids were not allowed. Paracetamol was recommended if pain relief was necessary; no pain medication was allowed in the 6 h before joint examination.

Efficacy was assessed every 2 weeks between baseline and week 8 and every 4 weeks thereafter. Efficacy variables included: counts of tender and swollen joints (28-joint assessment); physician's and patient's overall assessments of rheumatoid arthritis activity on a 5-point scale ranging from 1 (very good) to 5 (very poor); tender and swollen joint scores based on a scale of 0 (none) to 3 (severe); duration of morning stiffness; pain intensity assessed on a visual analogue scale of 0 (no pain) to 10 (severe pain); values of Westergren ESR, CRP, and rheumatoid factor; and health assessment questionnaire. The Stanford health assessment questionnaire[27] was used in countries with documented language adaptations of the questionnaire (all participating countries except Slovenia).

Radiographs, masked for treatment and sequence, were assessed (by A L) according to the Larsen method, adapted for use in clinical trials.[28–30] Briefly, initial and final radiographs of 40 joints in the hands (wrists) and feet were scored on a scale of 0 to 5. The overall sum was then divided by 40 to give the mean Larsen score per joint. The number of eroded joints was also counted. The joint involvement was expressed as mean scores and eroded joint counts.

The primary outcome measures were the swollen and tender joint counts and the patient's and physician's overall assessments of disease activity. In addition, we assessed the proportion of patients showing a clinical response of at least 20% as defined by the American College of Rheumatology criteria.[30] These criteria require improvement of at least 20% in tender and swollen joint counts and in three or more of: patient's and physician's overall assessment of rheumatoid arthritis activity, pain intensity, health assessment questionnaire, and CRP or ESR. The proportions with a 50% response (ie, ≥50% in all five criteria) were also calculated.

We also assessed response by the Paulus criteria,[31] which require improvement of at least 20% in four of: tender and swollen joint counts, morning stiffness, ESR, and patient's and physician's overall assessments of rheumatoid arthritis activity. We calculated American College of Rheumatology treatment success rates, defined as the proportion of patients who successfully completed 24 weeks of treatment and met the 20% responder criteria at that time. The 20% response to treatment was further characterised by investigation of time to and duration of sustained response (response at three consecutive visits or ≥8 weeks of American College of Rheumatology 20% response).

Safety was monitored by physical examination, chest radiography, electrocardiography, blood pressure, pulse rate, body temperature, and bodyweight measurements. Standard haematological and biochemical tests and urine analysis were also done. The occurrence of adverse events was documented and included those spontaneously reported by patients as well as those elicited by general questioning. Investigators were instructed to record adverse events as primary events (ie, the diagnosis of an isolated symptom) and symptoms accompanying the primary event. Analyses of the adverse events were done on the basis of the primary events. A serious adverse event was defined as fatal, life-threatening, permanently disabling, necessitating hospital admission, congenital anomaly, cancer, or overdose.

Laboratory variables were analysed at a central laboratory by mean values, mean changes from baseline, and shifts from baseline values—ie, from normal (or abnormal) at baseline to abnormal (or normal) at endpoint.

Statistical analyses

The sample size estimated from the results of the phase II study,[22] incorporated a three/two/three ratio of at least 108 patients to receive leflunomide, at least 72 to receive placebo, and at least 108 to receive sulphasalazine. This sample size yielded the following power calculations for the primary efficacy outcomes: tender joint count, mean change 5·0, 96%; swollen joint count, mean change 3·5, 96%; and overall assessments, mean change 3·5, 88%. Differences in three of four variables between leflunomide and placebo would be detected at a significance level of α=0·0375 at 84% overall power. A sample-size calculation based on American College of Rheumatology 20% response would have required a slightly smaller number of

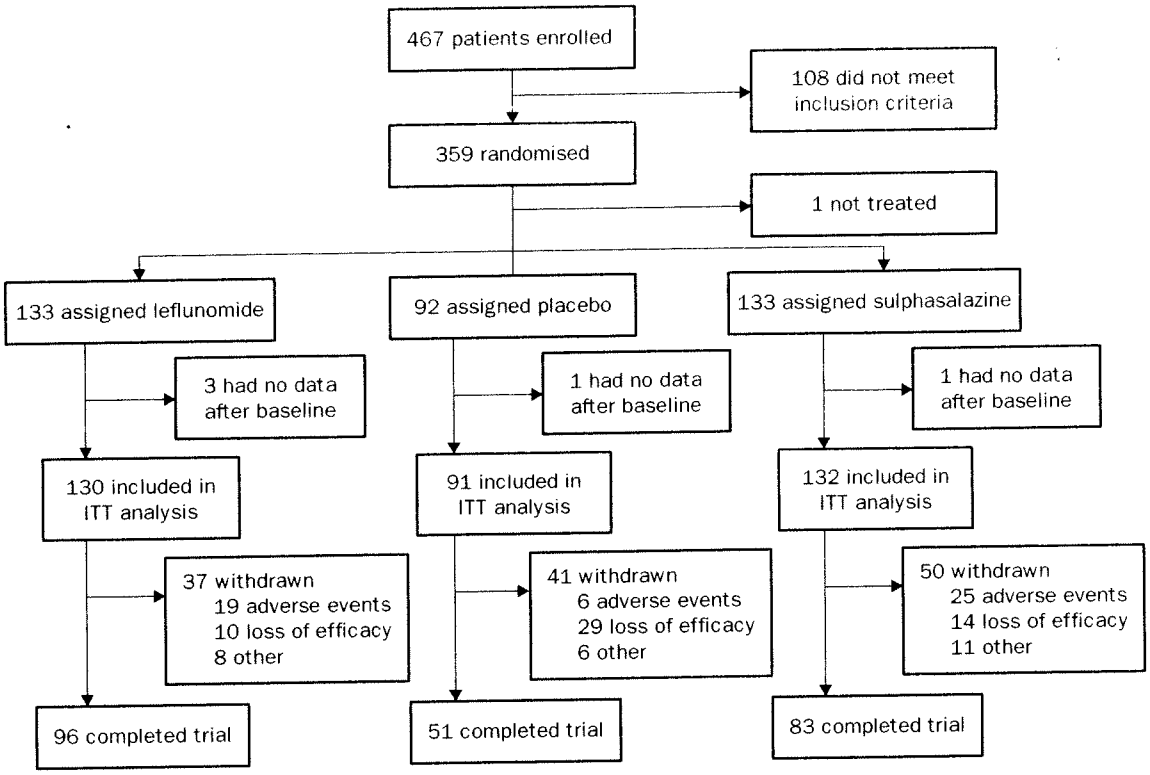

Figure 1: **Trial profile**
ITT=intention to treat.

patients. This study was not powered to show equivalence between the active treatments, and 95% CIs were used to describe the magnitude of the differences. Baseline categorical variables in the treatment groups were compared by means of χ^2 analysis or Fisher's exact test. Continuous variables were compared by ANOVA. Efficacy analysis of outcome variables was based on mean changes from baseline to endpoint in the intention-to-treat population with the technique of last observation carried forward and ANCOVA. Overall assessments were compared by means of the extended Mantel-Haenszel test. For radiographic analysis, only joints assessed at both baseline and endpoint were included in the analysis; endpoint was defined as the last value during the study or up to 2 months after last intake of study drug. In 13 patients in the leflunomide group, 20 in the placebo group, and 13 in the sulphasalazine group, the last radiographs were taken 15–57 days after last intake of study medication. Fewer patients (65% of the intention-to-treat population) were included in the radiographic analysis than in the efficacy analysis for various reasons, including missing or poor-quality radiographs. All laboratory variables were subjected to descriptive statistics and compared by means of the Wilcoxon signed-rank test. Rates of American College of Rheumatology response, Paulus response, and treatment success were analysed by logistic regression, adjusted for centre effect and disease duration. The randomisation code was broken only after the database was locked. All statistical tests were two-sided and significance was defined as $p<0.05$.

Results

Baseline characteristics of participants

The demographic characteristics of the treatment groups were similar (table 1). The mean age was 58 years (SD 12), and 72% of patients were women. The mean disease duration was 7 years; 41% of patients had had rheumatoid arthritis for 2 years or less. 93% of patients were of American College of Rheumatology functional class II or III. Across treatment groups, 40% to 53% of the patients had no history of DMARD treatment. The three groups were similar in terms of use of NSAIDs and corticosteroids and the proportion positive for rheumatoid factor.

Of 467 patients screened, 108 did not meet inclusion criteria (figure 1). One of the 359 randomised patients did not receive study medication. 128 patients withdrew early (28% leflunomide group, 45% placebo group, and 38% sulphasalazine group). The main reasons for early withdrawal were lack of efficacy (53 patients) and adverse events (50 patients). 25 patients withdrew for other reasons, such as protocol violations and non-compliance; one patient in the placebo group died of myocardial infarction. 230 patients completed 24 weeks of therapy. Treatment dose was lowered owing to an adverse event or abnormal laboratory-test result in four patients in the leflunomide group, nine in the sulphasalazine group, and three in the placebo group. The median dose of leflunomide (after day 3) was 20 mg daily, the median dose of sulphasalazine (after week 3) was 2 g daily.

Clinical efficacy

The decreases in variables assessed from baseline to week 24 were significantly greater with leflunomide than with placebo for all clinical outcome measures ($p<0.0001$, table 2).

Sequential changes in clinical and laboratory outcome measures are shown in figure 2. Mean values of most variables were significantly better in the leflunomide group than in the placebo group at 4, 12, and 24 weeks. On the health assessment questionnaire, the decrease in score in the leflunomide group was significantly greater than that in the sulphasalazine group at 4, 12, and 24 weeks. There were significant differences between the leflunomide and sulphasalazine groups at 4 weeks in tender and swollen joint counts, patient's and physician's overall assessments, pain intensity, rheumatoid factor,

Variable	Leflunomide (n=130)	Placebo (n=91)	Sulphasalazine (n=132)	p for leflunomide *vs* placebo	95% CI for leflunomide *vs* sulphasalazine
Tender joint count					
Baseline	18·8 (6·6)	16·3 (6·3)	16·7 (6·3)		
Change at endpoint	−9·7 (7·8)	−4·3 (7·5)	−8·1 (7·4)	0·0001	−2·42, 1·11
% change	52%	26%	48%		
Swollen joint count					
Baseline	16·2 (6·0)	15·8 (5·6)	15·3 (5·6)		
Change at endpoint	−7·2 (6·6)	−3·4 (6·5)	−6·2 (5·7)	0·0001	−2·19, 0·68
% change	44%	21%	40%		
Physician's assessment					
Baseline	3·6 (0·6)	3·5 (0·6)	3·5 (0·6)		
Change at endpoint	−1·1 (1·0)	−0·3 (1·0)	−1·0 (0·8)	0·001	−0·23, 0·21
% change	32%	9%	29%		
Patient's assessment					
Baseline	3·7 (0·7)	3·6 (0·7)	3·6 (0·7)		
Change at endpoint	−1·1 (1·1)	−0·4 (1·1)	−1·1 (1·0)	0·001	−0·28, 0·19
% change	30%	11%	31%		
ESR (mm/h)					
Baseline	55·7 (25·3)	52·3 (24·2)	50·5 (25·3)		
Change at endpoint	−7·4 (23·2)	3·4 (24·8)	−16·6 (24·0)	0·001	4·63, 15·5*
% change	13%	2%	33%		
Rheumatoid factor (U/mL)					
Baseline	349 (493)	331 (367)	369 (681)		
Change at endpoint	−141 (310)	17 (237)	−154 (379)	0·0001	−39·1, 66·8
% change	40%	5%	42%		
CRP (mg/L)					
Baseline	45 (42)	41 (45)	34 (31)		
Change at endpoint	−23 (35)	2 (37)	−11 (29)	0·0001	−10, 1
% change	51%	5%	32%		
Morning stiffness (min)					
Baseline	146 (197)	98 (85)	110 (99)		
Change at endpoint	−93 (250)	−68 (172)	−42 (158)	0·03	−56·4, 17·5
% change	65%	7%	38%		
Pain (VAS, mm)					
Baseline	63·3 (19·4)	58·9 (21·9)	55·1 (21·3)		
Change at endpoint	−27·3 (29·7)	−8·8 (29·9)	−19·8 (25·5)	0·0001	−8·0, 3·8
% change	43%	15%	36%		
Health assessment questionnaire					
Baseline	1·1 (0·6)	1·1 (0·6)	1·0 (0·6)		
Change at endpoint	−0·50 (0·5)	−0·04 (0·5)	−0·29 (0·5)	0·0001	−0·28, 0·04
% change	45%	4%	29%		

VAS=visual analogue scale. *p=0·04, leflunomide *vs* sulphasalazine; †p=0·009, leflunomide *vs* sulphasalazine.

Table 2: **Mean (SD) outcome measures (intention-to-treat population)**

and CRP. ESR fell by only 13% over 6 months with leflunomide but by 33% with sulphasalazine (p<0·04). However, the decrease in ESR with leflunomide was significantly (p<0·03) greater than the change with placebo throughout the study.

The numbers of patients responding to treatment as assessed by the American College of Rheumatology 20% criteria were 26 (29%) for placebo, 71 (55%) for leflunomide (p=0·0001 *vs* placebo), and 74 (56%) for sulphasalazine (p=0·0001 *vs* placebo). The response rates by the Paulus criteria also showed significant differences between active treatments and placebo (leflunomide 69 [53%], p=0·0001 *vs* placebo; sulphasalazine 75 [57%] p=0·0001 *vs* placebo; placebo 19 [21%]). Similar trends were observed with treatment success rate (American College of Rheumatology 20% at endpoint: leflunomide 62 [48%]; sulphasalazine 58 [44%]; placebo 26 [29%]). American College of Rheumatology 50% responder rates were 43 (33%) with leflunomide (p=0·002 *vs* placebo), 40 (30%) with sulphasalazine (p<0·003 *vs* placebo), and 13 (14%) with placebo.

Radiological disease progression

The Larsen score showed significantly less disease progression in the leflunomide and sulphasalazine groups than in the placebo group (table 3). Changes in eroded joint count were similar in the leflunomide and sulphasalazine groups (0·42 *vs* 0·41) and significantly lower than in the placebo group (1·4; p<0·001). The active treatment groups showed slower disease progression than the placebo group in the changes in subscores for the hands (leflunomide 0·01, sulphasalazine 0·01, placebo 0·05; p<0·025) and feet (leflunomide 0·01, sulphasalazine 0·02, placebo 0·06; p<0·025). American College of Rheumatology 20% response rates among patients included in the radiographic analysis were—leflunomide 57%, placebo 32%, and sulphasalazine 64%. The corresponding rates among those not included in the analysis were 49%, 23%, and 45%. This comparison shows that availability of radiographs did not favour the leflunomide group.

Onset of action

Significant decreases in all clinical outcome measures occurred sooner with leflunomide than with placebo, and effects were apparent as early as week 4 (figure 2). With leflunomide, the changes in most of these variables increased with time. In addition to the significant differences between the leflunomide and sulphasalazine groups in the decreases of all but two outcome measures at week 4 (figure 2), changes from baseline in CRP, rheumatoid factor, and health assessment questionnaire

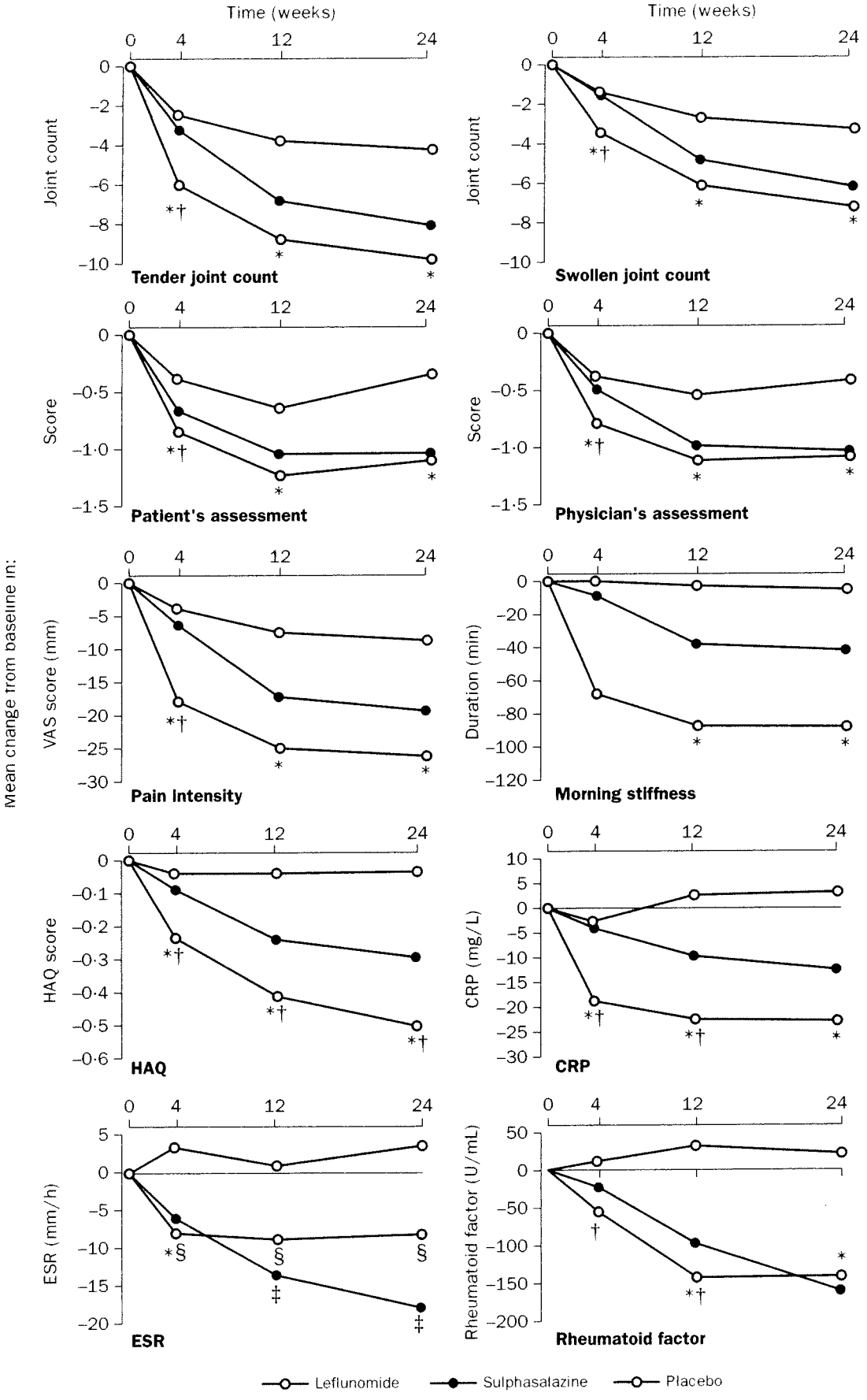

Figure 2: **Changes from baseline in outcome measures at weeks 4, 12, and 24**
*p≤0·001 *vs* placebo; †p≤0·03 *vs* sulphasalazine; ‡p<0·04 *vs* leflunomide; §p≤0·03 *vs* placebo.
VAS=visual analogue scale; HAQ=health assessment questionnaire.

	Leflunomide (n=91)	Placebo (n=60)	Sulphasalazine (n=77)
Baseline	1·48 (0·65)	1·49 (0·60)	1·39 (0·69)
Endpoint	1·49 (0·65)	1·54 (0·61)	1·40 (0·69)
Change at endpoint	0·01 (0·03)*	0·05 (0·09)	0·01 (0·03)*

Only joints evaluable at both baseline and endpoint included; endpoint was defined as last value on study or up to 2 months after last intake of study drug. To obtain traditional Larsen scores, † scores should be multiplied by the total number (40) of joints.
*$p \leq 0.001$ *vs* placebo.

Table 3: **Radiographic analysis of disease activity**

were also significantly greater at week 12, week 24, or both with leflunomide than with sulphasalazine.

The mean time to sustained response (American College of Rheumatology 20%) was 7·3 weeks with leflunomide, 10·1 weeks with placebo, and 8·3 weeks with sulphasalazine. Sustained response was achieved by 73 (56%) patients in the leflunomide group, 19 (21%) in the placebo group, and 66 (50%) in the sulphasalazine group (95% CI for differences: leflunomide *vs* placebo 23·3 to 47·2; leflunomide *vs* sulphasalazine −5·9 to 18·2; sulphasalazine *vs* placebo 17·2 to 41·1) The two active treatments were also similar in terms of the mean duration of sustained response (17·7 *vs* 17·0 weeks).

Safety

19 (14%) of 133 patients in the leflunomide group, six (7%) of 92 in the placebo group, and 25 (19%) of 133 in the sulphasalazine group were withdrawn because of adverse events. The most common adverse events related to leflunomide were diarrhoea, nausea, rash, and alopecia (table 4). Diarrhoea and alopecia were more frequent with leflunomide than with sulphasalazine. Nausea was the most common adverse event with sulphasalazine; five of these patients (and one each on leflunomide and placebo) were withdrawn; only one received antiemetic drugs to relieve nausea. Most of the patients with hypertension (except for one each in the leflunomide and placebo groups) had pre-existing high blood pressure. The overall frequency of serious adverse events possibly related to treatment was low in all three treatment groups (leflunomide 5%, placebo 5%, sulphasalazine 7%). There was one death (due to myocardial infarction) in the placebo group.

No clinically relevant abnormalities in electrolytes or haematological values were recorded in the leflunomide group. Leflunomide treatment did not affect serum creatinine concentrations but uric acid concentrations fell. In the leflunomide group, there were significant ($p \leq 0.01$) increases from baseline in haemoglobin (12·15 g/dL [7·57 mmol/L] to 12·55 g/dL [7·82 mmol/L]) and packed-cell volume (0·39 to 0·40%); these variables did not change significantly with placebo or sulphasalazine. Counts of leucocytes, neutrophils, and platelets decreased significantly ($p<0.0001$) from baseline to normal values with leflunomide and with sulphasalazine. Two cases of severe agranulocytosis and one of leucocytopenia were observed in the sulphasalazine group; both patients with agranulocytosis had infections and high fever. With discontinuation of sulphasasalazine in the patients with agranulocytosis, values fell to normal after a month in one patient, and the other recovered after treatment with granulocyte colony-stimulating factor.

Two patients in the leflunomide group, one in the placebo group, and two in the sulphasalazine group were withdrawn because they had abnormal results on liver function tests. One of the withdrawn leflunomide-group patients had hepatitis; however, many repeated tests gave no indication of a viral origin. Very abnormal values (three or more times the upper limit of normal) in liver function tests (alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase) were observed in three leflunomide-group patients and five sulphasalazine-group patients but no patient in the placebo group. Only one case (in the sulphasalazine group) was judged a serious adverse event. The proportion of patients with high values on liver function tests was similar with leflunomide and sulphasalazine; most of these raised values were 1·2 to 2·0 times the upper limit of normal.

At endpoint, a slight weight loss was observed in the leflunomide group (mean loss 0·9 kg), which did not differ significantly from that seen with placebo (mean loss 0·4 kg). Weight changes at endpoint in the sulphasalazine group differed from those in the leflunomide group (gain of 0·7 kg *vs* loss of 0·9 kg, $p<0.0001$). During the study, bodyweight decreases of 10% or more were observed in six patients in the leflunomide group, five in the placebo group, and two in the sulphasalazine group.

	Leflunomide (n=133)		Placebo (n=92)		Sulphasalazine (n=133)	
	Total	Treatment-related	Total	Treatment-related	Total	Treatment-related
Diarrhoea	17	16	5	4	9	8
Respiratory infections	14	1	20	3	15	3
Rheumatoid arthritis flare*	11	1	17	7	14	4
Nausea	10	9	7	7	17	14
Rash	10	8	4	4	9	9
Alopecia	8	8	2	2	5	5
Back pain†	8	0	2	1	2	0
Accidental injury	7	0	5	0	1	0
Headache	7	6	5	2	11	8
Hypertension	6	2	3	1	4	2
Dyspepsia	5	4	8	2	9	9
Pruritus	5	4	4	3	3	3
Gastrointestinal pain	5	4	7	5	6	5

Only events that occurred in ≥5% of any group are shown.
*A flare of rheumatoid arthritis was indicated by several investigators as an adverse event. Although this may more appropriately be termed a lack of effect rather than an adverse event, the investigators' assignment was not changed. Moreover, in some centres, patients with flares were admitted to hospital, which by definition is a serious adverse event.
†Back pain was not colicky in nature and was not due to renal problems.

Table 4: **Adverse events (%)**

Discussion

In this study, leflunomide and sulphasalazine effectively and safely alleviated signs and symptoms of active rheumatoid arthritis.

Leflunomide inhibits de-novo pyrimidine synthesis, and may act selectively on activated autoimmune lymphocytes, such as those involved in the pathogenesis of rheumatoid arthritis.[15–17] However, other modes of action may also be involved,[32,33] and further studies are needed to elucidate the in-vivo mechanism of action in rheumatoid arthritis. During the short period of this trial, leflunomide slowed radiographic disease progression and improved functional ability without major toxic effects.

DMARDs have been used for rheumatoid arthritis for many years,[4] and sulphasalazine and methotrexate, have been used very widely since the 1970s and early 1980s, respectively.[4,5,10] These and other DMARDs have been used with some success for the treatment of rheumatoid arthritis and have been shown to decrease signs and symptoms in clinical studies.[4,5,9–10,26,34–36] Some DMARDs, including sulphasalazine, have also been shown to retard radiographic progression to differing degrees,[4,5] and this

study confirmed the beneficial effect of sulphasalazine in comparison with placebo. The effect of sulphasalazine on radiographic progression was reported for the standard dose of 2 g daily,[8] which was also used in our study.

Many patients have to discontinue treatment with DMARDs because it is not effective or because they cannot tolerate adverse effects.[4,5,10,13,14,34,36] Such patients may fare better on other drugs, and many have to be treated with several agents either consecutively or in combination.[4,5,11,12] After nearly a decade with no new DMARDs developed, our study suggests a new option with similar efficacy to sulphasalazine, though the study was not powered to demonstrate equivalence between the two active treatments. Preliminary data suggest that leflunomide also has efficacy in combination with methotrexate in patients unresponsive to methotrexate monotherapy.[37]

The radiographic data show that leflunomide can significantly slow disease progression and thus is a true DMARD. We emphasise that these results should be interpreted with caution, since radiographs were missing for substantial numbers of patients, and the frequencies of American College of Rheumatology response rates were higher among patients with available radiographs than among those with missing radiographs in all three treatment groups. The difference in response rate between patients with and without available radiographs was lower with leflunomide (8%) than with sulphasalazine (19%) or placebo (11%). Previous studies have shown that in patients with rheumatoid arthritis, sulphasalazine slows disease progression,[8,10,35] to a greater degree than observed with hydroxychloroquine.[8] Our study is one of the first reports of slowing of radiographic progression in the short term. This finding may be related to the high proportion of patients with disease duration of 2 years or less enrolled in this study.

Many DMARDs require several weeks to months before the onset of their action is seen. Leflunomide showed a rapid onset of action. This feature may improve rate of retention of patients on treatment. The loading dose of leflunomide, 100 mg administered on the first 3 days of therapy,[25] may contribute to the rapidity of response to leflunomide.

The outcome of rheumatoid arthritis is related to the extent of the acute-phase response.[38] Hence, the limitation of the acute-phase response is an integral component of activity criteria in rheumatoid arthritis and response criteria for efficacy of DMARDs.[30,39] Leflunomide treatment was associated with significant decreases in CRP and ESR. However, the fall in ESR was much less pronounced than that in CRP. The reason for this discrepancy is unclear. Similar observations have been reported for cyclosporin,[40] which acts mainly on T lymphocytes, and azathioprine, which does not lower ESR significantly despite its effects on most other variables.[41] However, CRP is one of the most reliable measures of the acute-phase response and is responsive to changes in tissue damage.[42]

Functional disability is the most important factor in the day-to-day life and activity of patients with rheumatoid arthritis. Our analyses of pain intensity and functional disability showed that the leflunomide group had significant improvement compared with the placebo group. The leflunomide group also showed improvements in scores on the health assessment questionnaire that were significantly better than those with sulphasalazine therapy at all time points tested. However, higher doses of sulphasalazine (up to 3 g daily) may be used in patients who do not respond to lower doses,[6,7] although toxic effects may be greater at higher[36] than at lower doses.[9,12] In our study, adverse events leading to withdrawal occurred in 19% of the sulphasalazine group, 14% of the leflunomide group, and 7% of the placebo group. By contrast, early withdrawal rates due to lack of efficacy were higher with placebo (32%) than with leflunomide (8%) or sulphasalazine (11%).

As in an earlier phase II trial,[22] leflunomide was well tolerated in this study, with a safety profile similar to that of sulphasalazine. Liver function tests on occasion showed transient abnormalities with leflunomide and with sulphasalazine. However, these abnormalities resolved with dose reduction and resulted in withdrawal of only two leflunomide-treated patients and two sulphasalazine-treated patients. There were no significant haematological toxic effects associated with leflunomide. By contrast, in the sulphasalazine group there were two cases of agranulocytosis, a well-known complication with this drug;[43] these cases were associated with infectious events but were reversible. The increases in haemoglobin, packed-cell volume, and erythrocyte counts, and the decreases in platelet counts observed with leflunomide treatment indicate benefit in counteracting events leading to the anaemia and thrombocytosis commonly associated with active rheumatoid arthritis. Leflunomide treatment did not affect serum creatinine but uric acid concentrations fell in the leflunomide group; leflunomide has a known uricosuric effect (F Roch-Ramel, unpublished observations). The cause of the weight loss with leflunomide, also seen in the phase II study,[22] is not known and further work is needed on this issue.

Long-term observations in large numbers of patients will be needed to ensure that there are no unexpected late or cumulative effects from leflunomide, and that benefit is sustained.

Our findings on the efficacy and safety of leflunomide coupled with a novel mode of action suggest that this drug may be a useful addition to the current management of rheumatoid arthritis.

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